Non-Renal Effects and the Risk Assessment of Environmental Cadmium Exposure

**Agneta Åkesson, Lars Barregard, Ingvar A. Bergdahl,
Gunnar F. Nordberg, Monica Nordberg, and Staffan Skerfving**

Non-Renal Effects and the Risk Assessment of Environmental Cadmium Exposure

Agneta Åkesson,[1] Lars Barregard,[2] Ingvar A. Bergdahl,[3, 4] Gunnar F. Nordberg,[3] Monica Nordberg,[1] and Staffan Skerfving[5]

[1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [2]Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital and Academy, Gothenburg, Sweden; [3]Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, and [4]Department of Biobank Research, Umeå University, Umeå, Sweden; [5]Division of Occupational and Environmental Medicine, Department of Laboratory Medicine, University Hospital, Lund, Sweden

Address correspondence to A. Åkesson, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-17177 Stockholm, Sweden. Telephone: +46 8 52487542. E-mail: Agneta.Akesson@ki.se

Running title: Cadmium – a change in the risk assessment?

Competing Financial Interests: The authors declare they have no competing financial interests.

Abstract

Background: Exposure to cadmium (Cd) has long been recognized as a health hazard, both in industry and in general populations with high exposure. Under the currently prevailing health risk assessment, the relationship between urinary Cd concentrations (U-Cd) and tubular proteinuria is used. However, doubts have recently been raised regarding the justification of basing the risk assessment on this relationship at very low exposure.

Objectives: The objective of this paper is to review available information on health effects of Cd exposure with respect to human health risk assessment.

Discussion: The associations between U-Cd and U-proteins at very low exposure may not be due to Cd toxicity and the clinical significance of slight proteinuria may also be limited. More importantly, other effects have been reported at very low Cd exposure. There is reason to challenge the basis of the existing health risk assessment for Cd. Our review of the literature found that exposure to low concentrations of Cd is associated with effects on bone including increased risk of osteoporosis and fractures, and that this observation has implications for the health risk assessment of Cd. Other effects associated with Cd should also be considered, in particular cancer, though the information is still too limited for appropriate use in quantitative risk assessment.

Conclusion: Non-renal effects should be considered critical effects in the health risk assessment of Cd.

Introduction

Exposure to cadmium (Cd) has long been recognized as a health hazard, both in industry and in general populations with high exposure. There is widespread low-level Cd contamination of agricultural soil in many areas of the world. Because Cd is easily taken up by crops such as rice, wheat, vegetables, and potatoes, and occurs in high concentrations in shellfish, offal, and certain seeds, the exposure to Cd from food in many areas is high enough to be of importance to human health (EFSA 2009a; WHO 2011). Additional concern stems from the fact that exposure may not be decreasing, except in some areas that were once highly contaminated. Tobacco smoking further increases Cd exposure.

The toxic effects of Cd were initially considered to be limited to lung and kidney damage (occupational exposure) and kidney damage, osteomalacia, and fractures (dietary exposure; "itai-itai disease"; review by Nordberg et al. 2007). Until now, health risk assessment for both occupational exposure and long-term food-based exposure has been based on the effect on the kidney, with tubular proteinuria considered to be the critical effect in humans. According to the US Environmental Protection Agency the critical effect is the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases (US-EPAa). The dose-response assessment in the risk assessment process in humans relies on the relationship between Cd excreted in urine (U-Cd) and urinary markers of early renal tubular effects (EFSA 2009a; WHO 2011). In recent years, however, other Cd-related adverse effects have been reported at low-level environmental exposures. We aimed at reviewing the available information on these effects, to compare them with the kidney effects, and to indicate alternatives for risk assessors.

Toxicokinetics of cadmium

After uptake, Cd in blood plasma is bound to albumin and metallothionein (MT). Because of the small size of MT, Cd-MT is readily filtered through the glomeruli and reabsorbed by the proximal tubuli, and thus accumulates in the kidney cortex, where a major part of the body burden is located (Nordberg et al. 2007). Because the half-life of Cd in the kidney is > 10 years (Akerstrom et al. 2013a; Amzal et al. 2009) and a strong association is observed between concentrations of Cd in kidney and urine (Akerstrom et al. 2013a), the biomarker U-Cd reflects lifelong kidney accumulation which in turn mirrors the long-term total body burden. The majority of circulating Cd is bound in erythrocytes. Blood cadmium (B-Cd) is another possible biomarker of exposure. The shorter half-life of Cd in blood reflects change in exposure more closely than U-Cd (Liang et al. 2012). Numerous factors such as age, smoking status and gastrointestinal Cd absorption [low iron stores increase the absorption of Cd (Akesson et al. 2002; Berglund et al. 1994)] influence the relationship between dietary Cd exposure and U-Cd. Supplemental Material, Figure S1 shows the predicted relationship between estimated average long-term dietary Cd intake and the corresponding U-Cd as modeled for 50-year-old women with a constant daily Cd intake (Amzal et al. 2009).

Toxic effects of cadmium

Kidneys

Renal tubular dysfunction

Proteinuria is well-established as an adverse effect of Cd exposure. Long-term exposure resulting in U-Cd > 4 μg/g creatinine (cr) and/or B-Cd > 4 μg/L impairs renal tubular reabsorptive function, as shown by increased urinary excretion of low molecular weight proteins (LMWP)

such as β_2-microglobulin (B2M), α_1-microglobulin (A1M), and retinol-binding protein (EFSA 2009a; Jarup and Akesson 2009; Nordberg et al. 2007). The use of these LMWP as markers of adverse effect is supported by long-term follow-up surveys in Japan, where populations with Cd-induced tubular dysfunction had increased mortality in renal, cardiovascular, and cerebrovascular disorders, particularly when B2M exceeded 1000 µg/g cr (Nishijo et al. 2006).

To establish a dose-response relationship between U-Cd and B2M excretion, the European Food Safety Authority (EFSA) summarized the available data in a meta-analysis (EFSA 2009b). Both EFSA and the Joint FAO/WHO Committee on Food Additives and Contaminants modeled the relationships in their risk assessments (EFSA 2009a; WHO 2011) and used 4-5 µg Cd/g cr as the point when an increase in U-B2M was considered to occur, but arrived at different tolerable intakes. A weakness of both risk assessments is the fact that several studies of high quality were excluded from the meta-analysis, either because they used 24-hour urine sampling (instead of expressing the excretion per gram of cr in spot samples), or because they did not use U-B2M at all due to its susceptibility to breakdown at low urinary pH.

Several studies have reported positive associations between U-Cd and excretion of B2M (Chen et al. 2006b; Hong et al. 2004; Olsson et al. 2002) and other LWMP (Akesson et al. 2005; de Burbure et al. 2006; Jarup et al. 2000), at concentrations below U-Cd of 4-5 µg/g cr, even at U-Cd as low as < 1 µg/g cr. One study also reported an association between LMWP and B-Cd < 1 µg/L (Akesson et al. 2005). Whether these associations represent a causal relationship is discussed in the section "Low-level urinary Cd, proteinuria and causality."

Glomerular dysfunction

Some studies have reported associations between low-level Cd exposure and estimated glomerular function in cross-sectional analyses. In 700 elderly women, estimated glomerular filtration rate (eGFR) based on serum cystatin C or serum creatinine was statistically significantly lower at U-Cd 0.75-1.0 µg/g cr than at U-Cd < 0.5 µg/g cr (Akesson et al. 2005; Suwazono et al. 2006). Moreover, eGFR was decreased at B-Cd > 1 µg/L compared to B-Cd < 0.5 µg/L (Akesson et al. 2005). Though the associations became non-significant in the relatively small subgroup of never-smokers, a trend still appeared. Navas-Acien et al. (2009) analyzed B-Cd data from > 14,000 individuals in the USA and found increased odds of low eGFR at B-Cd at > 0.6 µg/L (median 1 µg/L) compared to individuals with B-Cd < 0.2 µg/L (odds ratio [OR]: 1.32; 95% confidence interval [CI]: 1.04, 1.68), though no associations were observed for the much smaller subgroup for whom U-Cd data were available (Ferraro et al. 2010). The increased OR for B-Cd > 0.6 µg/L was not present among never-smokers (Navas-Acien et al. 2009). An association between B-Cd and low eGFR was also found among Korean women but not men (Hwangbo et al. 2011; Myong et al. 2012). Estimates of GFR from creatinine or Cystatin C in blood have been shown to be imprecise and biased when GFR is normal or near normal (Issa et al. 2008; Murata et al. 2011; Tent et al. 2010). Therefore, even if the studies on eGFR suggest associations with Cd levels, they do not provide definitive evidence of clinically relevant reduced GFR at low level Cd exposure.

Apart from a change in the GFR, proteinuria is the hallmark of glomerular disease and initially albumin excretion increases most. Albumin has a molecular size of about 65 kDa which is above the threshold in the basement barrier in the glomerulus. Thus elevated albumin in urine indicates

damage of the integrity of the barrier. Several studies have demonstrated increased excretion of urinary albumin (U-Alb) in Cd-exposed workers and populations (Bernard et al. 1979; Buchet et al. 1980; Chen et al. 2006a; Ferraro et al. 2010; Jin et al. 2004; Liang et al. 2012; Navas-Acien et al. 2009). In an environmentally exposed Chinese population, increased U-Alb was reversible over the 8 years following cessation of the consumption of Cd-contaminated rice and subsequent lower dietary exposure, but changes in the excretion of LMWP were not reversible (Liang et al. 2012).

Renal failure

Several studies of high Cd exposure have shown associations between U-Cd and mortality from renal diseases (Nakagawa et al. 2006; Nishijo et al. 2006). An increased risk of end-stage renal disease (ESRD) was found in an ecological Swedish study combining occupationally and environmentally exposed subjects residing in areas close to battery plants (Hellstrom et al. 2001). On the other hand, an ecological study in Japan showed no association between mortality associated with renal failure and Cd levels in local brown rice (Koizumi et al. 2010). Only one study of prospective design has been published on ESRD in relation to low-level Cd biomarkers (Sommar et al. 2013). This case-referent study did not find Cd concentrations in erythrocytes at baseline to be a statistically significant risk factor for ESRD, after adjustment for potential confounders.

Low-level urinary Cd, proteinuria and causality

It has been proposed that the associations observed between very low-level U-Cd and proteinuria may not be caused by cadmium toxicity (Bernard 2008). Alternative explanations for the

associations are confounding by smoking or co-excretion of Cd and proteins due to variation in renal physiology as discussed below.

Tobacco smoking substantially increases Cd exposure, and thereby both B-Cd and U-Cd. If smoking also causes proteinuria (Haddam et al. 2011) independently of the Cd content in smoke, then it is an important confounder. In occupationally exposed workers, a weaker positive association between LMWP and U-Cd has been observed in never-smokers as compared to smokers (Chaumont et al. 2011; Haddam et al. 2011).

There are physiological mechanisms that could potentially result in an association between excretion of Cd and LMWP, without Cd toxicity being the cause. After filtration through the glomeruli, LMWP competes with albumin (in small amounts) and Cd-MT for reabsorption in the proximal tubule. LMWP and Cd-MT seem to have similar affinity for tubular binding sites (Bernard 2008; Chaumont et al. 2012), and so normal physiological changes in renal tubular reabsorption function can cause a co-excretion of Cd and LMWP. Varying diuresis (urinary flow rate) is an example of such normal renal physiological variability (Akerstrom et al. 2013b). This mechanism could be the reason for associations between excretion of Cd and LMWP among healthy teenagers with very low U-Cd (Chaumont et al. 2012). There was also a positive association between the excretion of Cd, A1M, and albumin *within* individuals with very low U-Cd (< 1 µg/g cr) irrespective of adjustment for variation in dilution (Akerstrom et al. 2013b), Moreover, urine flow rate had a positive impact on the excretion of Cd. Thus, it is possible that normal physiological variability in renal reabsorption of LMWP *causes* the increase in U-Cd by inhibiting tubular uptake of MT-bound Cd; in other words, this is a possible case of reverse causality (Chaumont et al. 2012).

While there is no reason to question the effect of Cd exposure on renal tubules at high exposure (U-Cd > 4 µg/g cr), the associations observed at low levels could be influenced by the factors mentioned. In addition, other factors should be considered, such as the ability to synthesize MT and the occurrence of MT antibodies (Nordberg et al. 2012). Thus, although a toxic effect cannot be ruled out at exposures corresponding to U-Cd < 1 µg Cd/g cr (values that generally occur among non-smokers in many populations worldwide), normal physiology is likely to be an important determinant (Akerstrom et al. 2013b; Chaumont et al. 2012). This makes it difficult to interpret any associations.

The effects of renal physiology are most likely eliminated when B-Cd, instead of U-Cd, is used as a marker of Cd exposure in relation to kidney effects markers in urine. Studies using B-Cd and LMWP in never-smokers would shed light on this issue, but such studies are demanding as regards population size and analytical performance. One study observed a statistically significant association in never-smokers between B-Cd and LMWP excretion (U-A1M) within the normal range (Akesson et al. 2005). A U-Cd of 1 µg/g cr corresponds to a B-Cd of about 1 µg/L, though the variation is wide.

Although long-term Cd-induced tubular proteinuria (high U-B2M) may be a risk factor for renal failure and mortality (Nishijo et al. 2006), the public-health impact of Cd-related increases in biomarkers of tubular dysfunction within the normal range is unknown.

Bone

It has long been well-established that excessive exposure to Cd may cause itai-itai disease, which occurs after manifestation of kidney damage and leads to osteomalacia and/or osteoporosis with multiple fractures (Nordberg et al. 2007).

A long series of recent cross-sectional and prospective studies of different populations, mainly from Belgium, Sweden, the USA, and China - some of them very large - clearly demonstrate associations between Cd exposure and low bone mineral density, as well as increased risk of osteoporosis (Table 1). Most of these studies used dual-energy X-ray absorptiometry, and defined low bone mass/osteoporosis based on Z-score or T-score.

The relationship between osteoporosis and fracture risk is well-established (Mackey et al. 2007; Marshall et al. 1996); osteoporosis at a skeletal site is highly predictive of a fracture in the same area. The Cd-associated increased risk of osteoporosis observed in some studies is thus of concern (Alfven et al. 2000; Engstrom et al. 2011, 2012; Gallagher et al. 2008; Nawrot et al. 2010; Staessen et al. 1999; Wang et al. 2003; Wu et al. 2010) (Table 1).

Most bone studies have used U-Cd to explore associations (Table 1). Although these were present at very low exposure levels, it is not likely that they represent reverse causation, i.e. that the bone effects cause increased U-Cd, e.g. that bone-derived proteins bind Cd and are excreted into urine. In addition to the studies based on biomonitoring of exposure, two were based on dietary Cd exposure, combining individual food consumption data from a food-frequency questionnaire with data on Cd content in food (Engstrom et al. 2012; Thomas et al. 2011). Both observed associations with osteoporosis and/or fracture incidence, even though the exposure misclassification with this method is likely to be larger than for the biomarkers. Decreased bone mineral density with increasing B-Cd has been described in a few studies. In one of them, B-Cd was < 1 µg/L (corresponding to an average U-Cd < 1 µg/g cr), but the population included subjects with previously higher Cd exposure (Alfven et al. 2002). In another study, exposure levels were very high (> 20 µg/L; Nordberg et al. 2002). Nevertheless, the fact that associations

between Cd and effects on bone were observed by use of three different exposure assessment methods (urine, blood, and dietary intake) reduces the likelihood that the results were due to confounding.

Another aspect in the interpretation of the studies on bone effects is the potential confounding by smoking (Law and Hackshaw 1997; Ward and Klesges 2001). Since tobacco smoke may well contain other agents affecting bone mineral density and fracture risk, such potential confounding must be considered in order to understand the actual association between Cd exposure and risk. In addition, smoking cessation is associated with a beneficial effect on bone (Oncken et al. 2006), while U-Cd remains essentially the same. A few studies did stratify by smoking status, and observed significant associations (Akesson et al. 2006; Engstrom et al. 2011; Engstrom et al. 2012; Thomas et al. 2011) or close to significant associations (Gallagher et al. 2008; Table 1) between Cd and bone effect in never-smokers. Indeed, two studies, based on dietary Cd intake rather than U-Cd, even reported stronger association in never-smokers than in all participants/ever-smokers (Engstrom et al. 2012; Thomas et al. 2011). This strongly supports the likelihood of an association with Cd which is independent of tobacco smoke.

Four studies failed to establish any statistically significant Cd-related effect on bone mineral density (Table 1). These null findings may be partly due to very low and/or narrow distribution of exposure, limited statistical power, and perhaps too young an age among the study populations. A small study of 380 men and women aged 49–77 with low exposure showed no significant association between U-Cd and bone mineral density (Wallin et al. 2005). Another small study (170 women and 100 men, 18-79 years of age) from Poland showed significant associations between U-Cd and B-Cd, on the one hand, and markers of bone mineral density, on

the other; but the association became non-significant after adjustment (Trzcinka-Ochocka et al. 2009). The relatively young age of the participants may have contributed to the lack of significant associations. Horiguchi et al. (2005) did not observe any association between Cd (blood and urine) and bone mineral density in 1,243 women consuming rice with varying contamination by Cd. However, since the statistical model could have resulted in over-adjustment, the results are not conclusive. Finally, a study of 908 Swedish women found that bone mineral density and markers of bone metabolism were statistically significantly associated at low B-Cd (Rignell-Hydbom et al. 2009). However, after adjustment for smoking, there was no significant correlation, and the statistical power was too low for a meaningful exclusive analysis of the never-smokers. Hence, we consider these four studies as inconclusive.

The levels of exposure associated with decreased bone mineral density and increased risk of osteoporosis and fractures vary (Table 1). Cross-sectional and prospective studies reported associations at U-Cd levels of 0.5–2 µg/g cr.

The mechanisms of bone effects considered secondary to the kidney damage include deficient reabsorption of calcium in the renal tubuli and compromised activation of vitamin D in the renal cortex. Several of the studies of bone effects also assessed kidney effects in parallel. The current understanding is that kidney effects are important in high exposure situations (Jin et al. 2004), while the osteoporosis observed at low Cd exposure may be independent of kidney effects (Akesson et al. 2006; Nawrot et al. 2010; Schutte et al. 2008). In accordance with this, there was no association between circulating concentrations of the active metabolite of vitamin D, on the one hand, and U-Cd or markers of bone metabolism, on the other, in women with relatively low

Cd exposure, despite significant associations between U-Cd and bone mineral density and bone metabolic markers (Engstrom et al. 2009).

There is growing evidence that Cd has a direct toxic effect on bone. Cd accumulates in osteocytes, the periosteum, and bone marrow, but not in the hydroxyapatite (Lindh et al. 1981). Experimental studies demonstrate skeletal effects of Cd *in vitro*, as well as *in vivo* in animals displaying no nephrotoxicity (Bhattacharyya 2009; Nordberg et al. 2007). Osteoclasts in culture are particularly sensitive to low Cd concentrations (Bhattacharyya 2009). In accordance with this, cross-sectional investigations have found a positive association between U-Cd and markers of bone resorption (Akesson et al. 2006; Schutte et al. 2008) (Table 1), even in children (Sughis et al. 2011). As a consequence of increased release of calcium from bone to the circulation, the excess is excreted into urine. Because U-Cd was inversely associated with levels of parathyroid hormone (Akesson et al. 2006; Schutte et al. 2008), the Cd-associated calciuria is most likely a result of increased bone resorption, rather than decreased tubular reabsorption, which would instead have resulted in a compensatory increase in parathyroid hormone.

The effect of Cd on the skeleton has been reported to be irreversible upon cessation of exposure. A longitudinal study from contaminated areas in China examined individuals living in areas with moderate (0.51 mg/kg) and heavy (3.7 mg/kg) exposure after cessation of consuming Cd-polluted rice (Chen et al. 2009). The decrease in wrist bone mineral density in women over 8 years was larger when baseline U-Cd and B-Cd were high, as compared to the low-exposure groups.

In conclusion, the data point toward a direct effect of Cd on bone. Even in the absence of Cd-induced renal tubular dysfunction, low-level environmental exposure to Cd seems to mobilize

bone minerals from the skeletal tissue. Effects on bone mineral density, osteoporosis and increased fracture risk, are reported to occur at U-Cd levels as low as 0.5-2 µg/g cr (Åkesson et al. 2006; Alfven et al. 2000, 2004; Engström et al. 2011; Gallagher et al. 2008; Nawrot et al. 2010; Shutte et al. 2008; Stassen et al. 1999; Wu et al. 2010). Similar associations have been observed at the corresponding dietary intakes (Engström et al. 2012; Thomas et al. 2011). Associations were also observed in studies where tobacco smoking could not be the cause (Åkesson et al. 2006; Engström et al. 2011, 2012; Thomas et al, 2011). The bone effects at high exposures appear not to be reversible (Chen et al, 2009).

Fragility fractures represent a considerable public-health problem, causing suffering as well as a burden to the individual and the society (Strom et al. 2011). Hence, fractures are much more severe health outcomes than decrease of bone mineral density and sub-clinical osteoporosis, for the individual and on the population level. The population attributable risk of dietary Cd for osteoporotic fractures was estimated to be about 7% and 13% in women and men, respectively (Engstrom et al. 2012; Thomas et al. 2011) in Sweden, where the exposure to Cd is at the low end in a global perspective (Hruba et al. 2012; Pawlas et al. 2013; Wennberg et al. 2006).

Cancer

The International Agency for Research on Cancer (IARC) in their most recent evaluation (IARC 2012) reconfirmed that there is sufficient evidence of Cd being a human carcinogen, mainly based on lung cancer in studies of workers

Studies of Cd exposure and cancer in the general population have found positive associations. In a Belgian prospective cohort of 994 persons (Nawrot et al. 2006), 24-hour U-Cd was associated with increased risk of lung cancer (relative risk [RR]: 1.70; 95% CI: 1.13, 2.57 for a doubling of

U-Cd [median 1.1 µg/24 h]), simultaneously adjusted for (*inter alia*) smoking and arsenic exposure. The risk was also increased in a geographical area with high Cd pollution, as compared to one with low, and in relation to the Cd concentrations in soil, though confounding by arsenic exposure cannot be ruled out. A Belgian case-control study of bladder cancer showed an increased risk even after adjustment for smoking (OR: 5.7; 95% CI: 3.3, 9.9) in subjects with high B-Cd (> 1 µg/L) as compared to low (< 0.2 µg/L) (Kellen et al. 2007).

Several mechanisms have been proposed for Cd-induced carcinogenicity, such as aberrant gene expression, oxidative stress, inhibition of DNA damage repair (Jin et al. 2003), apoptosis (Joseph 2009), and epigenetic alterations (Arita and Costa 2009). A factor of particular interest is that Cd may mimic the *in vivo* effects of estrogen in reproductive tissues (Ali et al. 2010; Ali et al. 2012; Byrne et al. 2009; Johnson et al. 2003). Present evidence does not allow a quantification of estrogenic risks (Kortenkamp 2011), but hormone-related cancers may still be of special concern.

In two very large population-based cohorts of Swedish men or postmenopausal women with an estimated average dietary Cd intake of 15 µg/day for women and 19 µg/day for men (women: 1.6 µg/kg body weight per week; men 1.7 µg/kg), statistically significantly increased incidences of endometrial (RR 1.39; 95% CI: 1.04, 1.86), breast (RR 1.21; 95% CI: 1.07, 1.36), and prostate (RR 1.13; CI 1.03, 1.24) cancer (but not ovarian cancer) were observed in those in the highest tertiles of Cd exposure (Akesson et al. 2008; Julin et al. 2011; Julin et al. 2012a; Julin et al. 2012b). Among never-smoking, non-overweight women without postmenopausal hormonal use, those who had a Cd intake above the median on two occasions 10 years apart had a RR of 2.9 (95% CI: 1.05, 7.79) for endometrial cancer (Åkesson et al. 2008). The median U-Cd in these never smoking women (1,225 women) was 0.29 µg/g cr (5th to 95th percentiles 0.15 to 0.79 µg/g

cr; Engström et al. 2011). In contrast, estimated dietary Cd exposure was not associated with the incidence of either total cancers or specific cancers in 90,000 Japanese men and women (Sawada et al. 2012), or with postmenopausal breast cancer incidence in 30,000 women in the USA (Adams et al. 2012a). However, the National Health and Nutrition Examination Survey (NHANES) prospectively showed higher uterine and total cancer mortality with increasing U-Cd (Adams et al. 2012b). Four case-control studies have been performed on breast cancer, all showing statistically significant increased odds with increasing U-Cd (Gallagher et al. 2010; McElroy et al. 2006; Nagata et al. 2013). Including 246 breast cancer cases, McElroy et al. (2006), observed a multivariable-adjusted OR of 2.29 (95% CI: 1.3, 4.2), comparing the highest quartile of U-Cd (> 0.58 µg/g cr) with the lowest (< 0.26 µg/g cr) (McElroy et al. 2006). Based on 153 breast cancer cases, Nagata et al. (2013) observed an OR of 6.05 (95% CI: 2.90, 12.62) comparing the highest tertile of U-Cd (> 2.6 µg/g) to lowest (< 1.7 µg/g) (Nagata et al. 2013). Similar results were observed in two other case-control samples from the USA, consisting of 100 and 98 cases, respectively (Gallagher et al. 2010). Data on premenopausal mammographic density, a strong marker of breast cancer risk, suggest a positive association with U-Cd (Adams et al. 2011); this lends support to the association between Cd and breast cancer risk.

In conclusion, Cd is carcinogenic, and some (but not all) recent data suggest an association with certain cancer forms even at the low dietary exposures encountered in the general population. The association is present even when smoking is taken into consideration, or when only never-smokers are studied. It appears that lung cancer and estrogen-dependent cancers are of particular importance.

Other effects

Cadmium is suspected to cause several other adverse health effects in humans, also at exposure levels found in the general population, but results have not been consistent or causality had not been definitely proven. Examples are neurodevelopmental effects (Cao et al. 2009; Ciesielski et al. 2012; Kippler et al. 2012a; Kippler et al. 2012b), diabetes (Afridi et al. 2008; Barregard et al. 2013; Schwartz et al. 2003), and cardiovascular disease or mortality (Agarwal et al. 2011; Bao et al. 2009; Fagerberg et al. 2012, 2013; Li et al. 2011; Menke et al. 2009; Messner et al. 2009; Nakagawa et al. 2006; Nawrot et al. 2008; Nishijo et al. 2006; Peters et al. 2010; Tellez-Plaza et al. 2012b; Tellez-Plaza et al. 2013)

Discussion

Tubular proteinuria is a well-established adverse effect associated with Cd exposure at U-Cd > 4 µg/g cr and/or B-Cd > 4 µg/L in occupationally as well as environmentally exposed populations. Such Cd-induced proteinuria has been associated with increased mortality in renal and cardiovascular diseases. However, in recent years, a considerable number of publications have presented evidence of an association between increased urinary excretion of proteins and the much lower U-Cd levels found in general populations. However, the apparent dose-response relationship for proteinuria at these low U-Cd levels may be non-causal (Akerstrom et al. 2013b; Haddam et al. 2011). Evidence of risk of chronic kidney disease (ESRD) at such low exposure is very limited.

Associations with bone effects, including a decrease of bone mineral density and increased risk of osteoporotic fractures, seem to occur at low Cd exposures. In this case, associations based on U-Cd are more conclusive than in the case of proteinuria mentioned above, at least in studies of

17

never-smokers. In addition, low-level dietary Cd exposure (about 15 µg/day), assessed from dietary questionnaires, has been associated with bone effects; this further supports a causal relationship between low level exposure and adverse effects on bone. These effects are also of greater public-health concern than increased urinary protein excretion.

The available information shows that associations with bone effects occur in population strata with low dietary Cd intake, corresponding to U-Cd as low as 0.5-2 µg/g cr. Such exposure is greatly exceeded in large populations in many parts of the world, and is present even in the areas with the lowest exposure range, such as the USA (Tellez-Plaza et al. 2012a) and Europe (Pawlas et al. 2013). A formal risk assessment based on bone effects is relevant and feasible, but out of the scope of this paper, but it is obvious that the more serious nature of bone effects compared to a slight tubular proteinuria should be considered in the health risk assessment. This could result in much lower tolerable intake, thus lower than the present US-EPA (1 µg/kg body weight and day; US-EPAb) and JECFA (25 µg/kg body weight and month; WHO, 2011) recommendations and possibly lower than the EFSA recommendations (2.5 µg/kg body weight and week; EFSA, 2009).

Cd is classified as a human carcinogen, and recent data have shown associations between low-level environmental Cd exposure and several forms of human tumors, (lung, kidney, bladder, endometrial, and breast cancer). It is possible that for such common cancers, even a slight increase of risk will carry a considerable public-health burden.

Hence, based on the available information, we suggest that Cd health risk assessment for the general population should consider effects other than proteinuria. Adverse effects on bone apparently occur at lower exposure than on the kidney (U-Cd 0.5-2 *vs* > 4 µg/g cr). The effects

are also more important for public health. Though the available information on risk is more limited than for proteinuria, it is still sufficient for a meaningful risk assessment. Data quoted above strongly indicate that estimates of the risks of bone effects in never-smoking, elderly women at present constitute the most substantial information on which estimates of exposure-response considerations may be based. At the same time, for future risk assessments, there is a need for more information on other non-renal effects (including cancer), with reliable data on low-level dietary exposure and/or body burden.

Agricultural soils are widely contaminated with Cd to such a degree that vegetable crops accumulate the element in concentrations sufficiently high to be a threat to public health. Also, this exposure has not decreased over the last decades, at least not in women (Wennberg et al. 2006). The situation here is thus quite different from exposure to lead (Stromberg et al. 2008; Wennberg et al. 2006) or mercury (Wennberg et al. 2006). Balance studies of Cd in topsoils indicate that the input usually exceeds the removal, at least in Europe (WHO 2007). The removal is very slow, and therefore any addition of Cd has long-lasting consequences, and so it is important to strictly reduce any further addition of Cd. Cd input to agricultural soil mainly originates from Cd-containing phosphate fertilizers and industrial emissions, the latter resulting in long-range trans-boundary transport with deposition far from the source (WHO 2007).

Conclusions

Current information urges a shift in the strategy for assessment of Cd risks in the general population, moving away from a unique focus on renal tubular proteinuria. It is likely that, at present, bone effects will contribute more than kidney effects to the overall risk, suggesting that such effects should be an additional basis for health risk assessment.

References

Adams SV, Newcomb PA, Shafer MM, Atkinson C, Bowles EJ, Newton KM, et al. 2011. Urinary cadmium and mammographic density in premenopausal women. Breast Cancer Res Treat 128:837-844.

Adams SV, Newcomb PA, White E. 2012a. Dietary cadmium and risk of invasive postmenopausal breast cancer in the VITAL cohort. Cancer Causes Control 23:845-854.

Adams SV, Passarelli MN, Newcomb PA. 2012b. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. Occup Environ Med 69:153-156.

Afridi HI, Kazi TG, Kazi N, Jamali MK, Arain MB, Jalbani N, et al. 2008. Evaluation of status of toxic metals in biological samples of diabetes mellitus patients. Diabetes Res Clin Pract 80:280-288.

Agarwal S, Zaman T, Tuzcu EM, Kapadia SR. 2011. Heavy metals and cardiovascular disease: results from the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Angiology 62:422-429.

Akerstrom M, Barregard L, Lundh T, Sallsten G. 2013a. The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. Toxicol Appl Pharmacol 268:286-293.

Akerstrom M, Sallsten G, Lundh T, Barregard L. 2013b. Associations between urinary excretion of cadmium and proteins in a nonsmoking population: renal toxicity or normal physiology? Environ Health Perspect 121:187-191.

Akesson A, Berglund M, Schutz A, Bjellerup P, Bremme K, Vahter M. 2002. Cadmium exposure in pregnancy and lactation in relation to iron status. Am J Public Health 92:284-287.

Akesson A, Lundh T, Vahter M, Bjellerup P, Lidfeldt J, Nerbrand C, et al. 2005. Tubular and glomerular kidney effects in Swedish women with low environmental cadmium exposure. Environ Health Perspect 113:1627-1631.

Akesson A, Bjellerup P, Lundh T, Lidfeldt J, Nerbrand C, Samsioe G, et al. 2006. Cadmium-induced effects on bone in a population-based study of women. Environ Health Perspect 114:830-834.

Akesson A, Julin B, Wolk A. 2008. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. Cancer research 68:6435-6441.

Alfven T, Elinder CG, Carlsson MD, Grubb A, Hellstrom L, Persson B, et al. 2000. Low-level cadmium exposure and osteoporosis. J Bone Miner Res 15:1579-1586.

Alfven T, Jarup L, Elinder CG. 2002. Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. Environ Health Perspect 110:699-702.

Alfven T, Elinder CG, Hellstrom L, Lagarde F, Jarup L. 2004. Cadmium exposure and distal forearm fractures. J Bone Miner Res 19:900-905.

Ali I, Penttinen-Damdimopoulou PE, Makela SI, Berglund M, Stenius U, Akesson A, et al. 2010. Estrogen-Like Effects of Cadmium *in vivo* do not Appear to be Mediated via the Classical Estrogen Receptor Transcriptional Pathway. Environ Health Perspect 118:1389-1394.

Ali I, Damdimopoulou P, Stenius U, Adamsson A, Makela SI, Akesson A, et al. 2012. Cadmium-induced effects on cellular signaling pathways in the liver of transgenic estrogen reporter mice. Toxicol Sci 127:66-75.

Amzal B, Julin B, Vahter M, Wolk A, Johanson G, Akesson A. 2009. Population toxicokinetic modeling of cadmium for health risk assessment. Environ Health Perspect 117:1293-1301.

Arita A, Costa M. 2009. Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. Metallomics 1:222-228.

Bao QS, Lu CY, Song H, Wang M, Ling W, Chen WQ, et al. 2009. Behavioural development of school-aged children who live around a multi-metal sulphide mine in Guangdong province, China: a cross-sectional study. BMC Public Health 9:217.

Barregard L, Bergstrom G, Fagerberg B. 2013. Cadmium exposure in relation to insulin production, insulin sensitivity and type 2 diabetes: a cross-sectional and prospective study in women. Environ Res 121:104-109.

Berglund M, Akesson A, Nermell B, Vahter M. 1994. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ Health Perspect 102:1058-1066.

Bernard A, Buchet JP, Roels H, Masson P, Lauwerys R. 1979. Renal excretion of proteins and enzymes in workers exposed to cadmium. Eur J Clin Invest 9:11-22.

Bernard A. 2008. Cadmium & its adverse effects on human health. Indian J Med Res 128:557-564.

Bhattacharyya MH. 2009. Cadmium osteotoxicity in experimental animals: mechanisms and relationship to human exposures. Toxicol Appl Pharmacol 238:258-265.

Buchet JP, Roels H, Bernard A, Lauwerys R. 1980. Assessment of renal function of workers exposed to inorganic lead, calcium or mercury vapor. J Occup Med 22:741-750.

Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. 2009. Cadmium - a metallohormone? Toxicol Appl Pharmacol 238:266-271.

Cao Y, Chen A, Radcliffe J, Dietrich KN, Jones RL, Caldwell K, et al. 2009. Postnatal cadmium exposure, neurodevelopment, and blood pressure in children at 2, 5, and 7 years of age. Environ Health Perspect 117:1580-1586.

Chaumont A, De Winter F, Dumont X, Haufroid V, Bernard A. 2011. The threshold level of urinary cadmium associated with increased urinary excretion of retinol-binding protein and beta 2-microglobulin: a re-assessment in a large cohort of nickel-cadmium battery workers. Occup Environ Med 68:257-264.

Chaumont A, Nickmilder M, Dumont X, Lundh T, Skerfving S, Bernard A. 2012. Associations between proteins and heavy metals in urine at low environmental exposures: evidence of reverse causality. Toxicol Lett 210:345-352.

Chen L, Jin T, Huang B, Nordberg G, Nordberg M. 2006a. Critical exposure level of cadmium for elevated urinary metallothionein--an occupational population study in China. Toxicol Appl Pharmacol 215:93-99.

Chen L, Lei L, Jin T, Nordberg M, Nordberg GF. 2006b. Plasma metallothionein antibody, urinary cadmium, and renal dysfunction in a Chinese type 2 diabetic population. Diabetes Care 29:2682-2687.

Chen X, Zhu G, Jin T, Akesson A, Bergdahl IA, Lei L, et al. 2009. Changes in bone mineral density 10 years after marked reduction of cadmium exposure in a Chinese population. Environ Res 109:874-879.

Ciesielski T, Weuve J, Bellinger DC, Schwartz J, Lanphear B, Wright RO. 2012. Cadmium
exposure and neurodevelopmental outcomes in U.S. children. Environ Health Perspect
120:758-763.

de Burbure C, Buchet JP, Leroyer A, Nisse C, Haguenoer JM, Mutti A, et al. 2006. Renal and
neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early
effects and multiple interactions at environmental exposure levels. Environ Health Perspect
114:584-590.

EFSA European Food Safety Authority. 2009a. Scientific Opinion; Cadmium in food. (The
EFSA Journal (2009) 980, 1-139).

EFSA European Food Safety Authority. 2009b. Meta-analysis of Dose-Effect Relationship of
Cadmium for Benchmark Dose Evaluation. (EFSA Scientific Report (2009) 254, 1-62).

Engstrom A, Skerving S, Lidfeldt J, Burgaz A, Lundh T, Samsioe G, et al. 2009. Cadmium-
induced bone effect is not mediated via low serum 1,25-dihydroxy vitamin D. Environ Res
109:188-192.

Engstrom A, Michaelsson K, Suwazono Y, Wolk A, Vahter M, Akesson A. 2011. Long-term
cadmium exposure and the association with bone mineral density and fractures in a
population-based study among women. J Bone Miner Res 26:486-495.

Engstrom A, Michaelsson K, Vahter M, Julin B, Wolk A, Akesson A. 2012. Associations
between dietary cadmium exposure and bone mineral density and risk of osteoporosis and
fractures among women. Bone 50:1372-1378.

Fagerberg B, Bergstrom G, Boren J, Barregard L. 2012. Cadmium exposure is accompanied by
increased prevalence and future growth of atherosclerotic plaques in 64-year-old women. J
Intern Med 272:601-610.

Fagerberg B, Bergstrom G, Boren J, Barregard L. 2013. Cadmium exposure, intercellular
adhesion molecule-1 and peripheral artery disease: a cohort and an experimental study. BMJ
Open 3.

Ferraro PM, Costanzi S, Naticchia A, Sturniolo A, Gambaro G. 2010. Low level exposure to
cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999-2006.
Bmc Public Health 10.

Gallagher CM, Kovach JS, Meliker JR. 2008. Urinary cadmium and osteoporosis in U.S. Women >or= 50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect 116:1338-1343.

Gallagher CM, Chen JJ, Kovach JS. 2010. Environmental cadmium and breast cancer risk. Aging 2:804-814.

Haddam N, Samira S, Dumont X, Taleb A, Lison D, Haufroid V, et al. 2011. Confounders in the assessment of the renal effects associated with low-level urinary cadmium: an analysis in industrial workers. Environ Health 10:37.

Hellstrom L, Elinder CG, Dahlberg B, Lundberg M, Jarup L, Persson B, et al. 2001. Cadmium exposure and end-stage renal disease. Am J Kidney Dis 38:1001-1008.

Honda R, Tsuritani I, Noborisaka Y, Suzuki H, Ishizaki M, Yamada Y. 2003. Urinary cadmium excretion is correlated with calcaneal bone mass in Japanese women living in an urban area. Environ Res 91:63-70.

Hong F, Jin T, Zhang A. 2004. Risk assessment on renal dysfunction caused by co-exposure to arsenic and cadmium using benchmark dose calculation in a Chinese population. Biometals 17:573-580.

Horiguchi H, Oguma E, Sasaki S, Miyamoto K, Ikeda Y, Machida M, et al. 2005. Environmental exposure to cadmium at a level insufficient to induce renal tubular dysfunction does not affect bone density among female Japanese farmers. Environ Res 97:83-92.

Hruba F, Stromberg U, Cerna M, Chen C, Harari F, Harari R, et al. 2012. Blood cadmium, mercury, and lead in children: an international comparison of cities in six European countries, and China, Ecuador, and Morocco. Environ Int 41:29-34.

Hwangbo Y, Weaver VM, Tellez-Plaza M, Guallar E, Lee BK, Navas-Acien A. 2011. Blood cadmium and estimated glomerular filtration rate in Korean adults. Environ Health Perspect 119:1800-1805.

IARC International Agency for Research on Cancer. 2012. Cadmium and cadmium compounds. Available: http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-8.pdf 100].

Issa N, Meyer KH, Arrigain S, Choure G, Fatica RA, Nurko S, et al. 2008. Evaluation of creatinine-based estimates of glomerular filtration rate in a large cohort of living kidney donors. Transplantation 86:223-230.

Jarup L, Hellstrom L, Alfven T, Carlsson MD, Grubb A, Persson B, et al. 2000. Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup Environ Med 57:668-672.

Jarup L, Akesson A. 2009. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238:201-208.

Jin T, Nordberg G, Ye T, Bo M, Wang H, Zhu G, et al. 2004. Osteoporosis and renal dysfunction in a general population exposed to cadmium in China. Environ Res 96:353-359.

Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, et al. 2003. Cadmium is a mutagen that acts by inhibiting mismatch repair. Nat Genet 34:326-329.

Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, et al. 2003. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat Med 9:1081-1084.

Joseph P. 2009. Mechanisms of cadmium carcinogenesis. Toxicol Appl Pharmacol 238:272-279.

Julin B, Wolk A, Akesson A. 2011. Dietary cadmium exposure and risk of epithelial ovarian cancer in a prospective cohort of Swedish women. Br J Cancer 105:441-444.

Julin B, Wolk A, Bergkvist L, Bottai M, Akesson A. 2012a. Dietary cadmium exposure and risk of postmenopausal breast cancer: a population-based prospective cohort study. Cancer research 72:1459-1466.

Julin B, Wolk A, Johansson JE, Andersson SO, Andren O, Akesson A. 2012b. Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study. Br J Cancer 107:895-900.

Kellen E, Zeegers MP, Hond ED, Buntinx F. 2007. Blood cadmium may be associated with bladder carcinogenesis: the Belgian case-control study on bladder cancer. Cancer detection and prevention 31:77-82.

Kippler M, Tofail F, Gardner R, Rahman A, Hamadani JD, Bottai M, et al. 2012a. Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study. Environ Health Perspect 120:284-289.

Kippler M, Tofail F, Hamadani JD, Gardner RM, Grantham-McGregor SM, Bottai M, et al. 2012b. Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. Environ Health Perspect 120:1462-1468.

Koizumi N, Ohashi F, Ikeda M. 2010. Lack of correlation between cadmium level in local brown rice and renal failure mortality among the residents: a nation-wide analysis in Japan. Int Arch Occup Environ Health 83:333-339.

Kortenkamp A. 2011. Are cadmium and other heavy metal compounds acting as endocrine disrupters? Met Ions Life Sci 8:305-317.

Law MR, Hackshaw AK. 1997. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ (Clinical research ed 315:841-846.

Li Q, Nishijo M, Nakagawa H, Morikawa Y, Sakurai M, Nakamura K, et al. 2011. Relationship between urinary cadmium and mortality in habitants of a cadmium-polluted area: a 22-year follow-up study in Japan. Chinese medical journal 124:3504-3509.

Liang Y, Lei L, Nilsson J, Li H, Nordberg M, Bernard A, et al. 2012. Renal function after reduction in cadmium exposure: an 8-year follow-up of residents in cadmium-polluted areas. Environ Health Perspect 120:223-228.

Lindh U, Brune D, Nordberg G, Wester PO. 1981. Levels of cadmium in bone tissue (femur) of industrially exposed workers - a reply. Sci Total Environ 20:3-11.

Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, et al. 2007. High-trauma fractures and low bone mineral density in older women and men. JAMA 298:2381-2388.

Marshall D, Johnell O, Wedel H. 1996. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ (Clinical research ed 312:1254-1259.

McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. 2006. Cadmium exposure and breast cancer risk. J Natl Cancer Inst 98:869-873.

Menke A, Muntner P, Silbergeld EK, Platz EA, Guallar E. 2009. Cadmium levels in urine and mortality among U.S. adults. Environ Health Perspect 117:190-196.

Messner B, Knoflach M, Seubert A, Ritsch A, Pfaller K, Henderson B, et al. 2009. Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. Arteriosclerosis, thrombosis, and vascular biology 29:1392-1398.

Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC. 2011. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. Clin J Am Soc Nephrol 6:1963-1972.

Myong JP, Kim HR, Baker D, Choi B. 2012. Blood cadmium and moderate-to-severe glomerular dysfunction in Korean adults: analysis of KNHANES 2005-2008 data. Int Arch Occup Environ Health 85:885-893.

Nagata C, Nagao Y, Nakamura K, Wada K, Tamai Y, Tsuji M, et al. 2013. Cadmium exposure and the risk of breast cancer in Japanese women. Breast Cancer Res Treat 138:235-239.

Nakagawa H, Nishijo M, Morikawa Y, Miura K, Tawara K, Kuriwaki J, et al. 2006. Urinary cadmium and mortality among inhabitants of a cadmium-polluted area in Japan. Environ Res 100:323-329.

Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, et al. 2009. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. Am J Epidemiol 170:1156-1164.

Nawrot T, Plusquin M, Hogervorst J, Roels HA, Celis H, Thijs L, et al. 2006. Environmental exposure to cadmium and risk of cancer: a prospective population-based study. Lancet Oncol 7:119-126.

Nawrot T, Geusens P, Nulens TS, Nemery B. 2010. Occupational cadmium exposure and calcium excretion, bone density, and osteoporosis in men. J Bone Miner Res 25:1441-1445.

Nawrot TS, Van Hecke E, Thijs L, Richart T, Kuznetsova T, Jin Y, et al. 2008. Cadmium-related mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. Environ Health Perspect 116:1620-1628.

Nishijo M, Morikawa Y, Nakagawa H, Tawara K, Miura K, Kido T, et al. 2006. Causes of death and renal tubular dysfunction in residents exposed to cadmium in the environment. Occup Environ Med 63:6.

Nordberg G, Jin T, Bernard A, Fierens S, Buchet JP, Ye T, et al. 2002. Low bone density and renal dysfunction following environmental cadmium exposure in China. Ambio 31:478-481.

Nordberg G, Jin T, Wu X, Lu J, Chen L, Liang Y, et al. 2012. Kidney dysfunction and cadmium exposure--factors influencing dose-response relationships. J Trace Elem Med Biol 26:197-200.

Nordberg GF, Nogawa K, Nordberg M, Friberg LT. 2007. Cadmium. In: Handbook on the Toxicology of Metals, Vol. Chapter 23, Part Third edition (Nordberg GF, Fowler B, Nordberg M, Friberg LT, eds):Academic Press, Elsevier, 445-486.

Olsson IM, Bensryd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. 2002. Cadmium in
blood and urine--impact of sex, age, dietary intake, iron status, and former smoking--
association of renal effects. Environ Health Perspect 110:1185-1190.

Oncken C, Prestwood K, Kleppinger A, Wang Y, Cooney J, Raisz L. 2006. Impact of smoking
cessation on bone mineral density in postmenopausal women. J Womens Health (Larchmt)
15:1141-1150.

Pawlas N, Stromberg U, Carlberg B, Cerna M, Harari F, Harari R, et al. 2013. Cadmium,
mercury and lead in the blood of urban women in Croatia, the Czech Republic, Poland,
Slovakia, Slovenia, Sweden, China, Ecuador and Morocco. Int J Occup Med Environ Health
26:58-72.

Peters JL, Perlstein TS, Perry MJ, McNeely E, Weuve J. 2010. Cadmium exposure in association
with history of stroke and heart failure. Environ Res 110:199-206.

Rignell-Hydbom A, Skerfving S, Lundh T, Lindh CH, Elmstahl S, Bjellerup P, et al. 2009.
Exposure to cadmium and persistent organochlorine pollutants and its association with bone
mineral density and markers of bone metabolism on postmenopausal women. Environ Res
109:991-996.

Sawada N, Iwasaki M, Inoue M, Takachi R, Sasazuki S, Yamaji T, et al. 2012. Long-term
dietary cadmium intake and cancer incidence. Epidemiology 23:368-376.

Schutte R, Nawrot TS, Richart T, Thijs L, Vanderschueren D, Kuznetsova T, et al. 2008. Bone
resorption and environmental exposure to cadmium in women: a population study. Environ
Health Perspect 116:777-783.

Schwartz GG, Il'yasova D, Ivanova A. 2003. Urinary cadmium, impaired fasting glucose, and
diabetes in the NHANES III. Diabetes Care 26:468-470.

Sommar JN, Svensson MK, Bjor BM, Elmstahl SI, Hallmans G, Lundh T, et al. 2013. End-stage
renal disease and low level exposure to lead, cadmium and mercury; a population-based,
prospective nested case-referent study in Sweden. Environ Health 12:9.

Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, et al. 1999.
Environmental exposure to cadmium, forearm bone density, and risk of fractures:
prospective population study. Public Health and Environmental Exposure to Cadmium
(PheeCad) Study Group. Lancet 353:1140-1144.

Strom O, Borgstrom F, Kanis JA, Compston J, Cooper C, McCloskey EV, et al. 2011. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 6:59-155.

Stromberg U, Lundh T, Skerfving S. 2008. Yearly measurements of blood lead in Swedish children since 1978: the declining trend continues in the petrol-lead-free period 1995-2007. Environ Res 107:332-335.

Sughis M, Penders J, Haufroid V, Nemery B, Nawrot TS. 2011. Bone resorption and environmental exposure to cadmium in children: a cross--sectional study. Environ Health 10:104.

Suwazono Y, Sand S, Vahter M, Filipsson AF, Skerfving S, Lidfeldt J, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Suwazono Y, Sand S, Vahter M, Skerfving S, Lidfeldt J, Akesson A. 2010. Benchmark dose for cadmium-induced osteoporosis in women. Toxicol Lett 197:123-127.

Tellez-Plaza M, Navas-Acien A, Caldwell KL, Menke A, Muntner P, Guallar E. 2012a. Reduction in cadmium exposure in the United States population, 1988-2008: the contribution of declining smoking rates. Environ Health Perspect 120:204-209.

Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. 2012b. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. Environ Health Perspect 120:1017-1022.

Tellez-Plaza M, Guallar E, Howard BV, Umans JG, Francesconi KA, Goessler W, et al. 2013. Cadmium exposure and incident cardiovascular disease. Epidemiology 24:421-429.

Tent H, Rook M, Stevens LA, van Son WJ, van Pelt LJ, Hofker HS, et al. 2010. Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. Clin J Am Soc Nephrol 5:1960-1968.

Thomas LD, Michaelsson K, Julin B, Wolk A, Akesson A. 2011. Dietary cadmium exposure and fracture incidence among men: A population-based prospective cohort study. J Bone Miner Res 26:1601-1608.

Trzcinka-Ochocka M, Jakubowski M, Szymczak W, Janasik B, Brodzka R. 2009. The effects of low environmental cadmium exposure on bone density. Environ Res 110:286-293.

US-EPAa, Environmental Protection Agency. Available at:
http://www.epa.gov/ttn/atw/toxsource/noncarcinogens.html. Risk Assessment for Noncancer
Effects. [accessed 27 January 2014].

US-EPAb, Environmental Protection Agency. Available at:
http://www.epa.gov/iris/subst/0141.htm#reforal. Integrated Risk Information System.
Cadmium. [accessed 27 January 2014].

Wallin E, Rylander L, Jonssson BA, Lundh T, Isaksson A, Hagmar L. 2005. Exposure to CB-153
and p,p'-DDE and bone mineral density and bone metabolism markers in middle-aged and
elderly men and women. Osteoporos Int 16:2085-2094.

Wang H, Zhu G, Shi Y, Weng S, Jin T, Kong Q, et al. 2003. Influence of environmental
cadmium exposure on forearm bone density. J Bone Miner Res 18:553-560.

Ward KD, Klesges RC. 2001. A meta-analysis of the effects of cigarette smoking on bone
mineral density. Calcif Tissue Int 68:259-270.

Wennberg M, Lundh T, Bergdahl IA, Hallmans G, Jansson JH, Stegmayr B, et al. 2006. Time
trends in burdens of cadmium, lead, and mercury in the population of northern Sweden.
Environ Res 100:330-338.

WHO World Health Organization. 2011. Evaluation of certain food additives and contaminants.
Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva.

WHO World Health Organization, Europe. 2007. Health risks of heavy metals from long-range
transboundary air pollution. Copenhagen.

Wu Q, Magnus JH, Hentz JG. 2010. Urinary cadmium, osteopenia, and osteoporosis in the US
population. Osteoporos Int 21:1449-1454.

Table 1. Studies of the relationship between cadmium exposure and bone effects.

Country; study population; sex	Age; no. of participants	Study design; bone effect measure	Threshold of bone effect	Smoking adjustment or stratification	Source
Studies with bone mineral density or osteoporosis as outcome					
Belgium; general population; men and women	mean 44 years; n=506	Prospective; density	Association with U-Cd (mean ~1.0 µg/g cr) in women. No threshold	No effect of smoking	(Staessen et al. 1999)
South Sweden; general population and battery workers; men and women	mean 41 and 44 years; n=1,064	Cross-sectional; osteoporosis (Z-score ≥1)	10% excess risk at U-Cd 0.5-3.0, compared to <0.5 µg/g cr	Adjusted	(Alfven et al. 2000)
Japan; general population; women	40-86 years; n=908	Cross-sectional; density (ultrasound; calcaneus stiffness)	Density negatively correlated with U-Cd (mean 2.9 µg/g cr)	No adjustment or stratification	(Honda et al. 2003)
China; general population in areas with varying contamination of rice; women and men	mean 50 and 55 years; n=790	Cross-sectional with longitudinal components; density and osteoporosis (T-Score ≥2.5)	Effects at mean U-Cd 2.3-13 µg/g cr. No observed reversibility (Chen et al, 2009)	Adjusted	(Chen et al. 2009; Jin et al. 2004; Wang et al. 2003)
Sweden; fishermen and their wives	median 59 and 62 years; n=380	Cross-sectional; density and biochemical markers	No association with U-Cd (medians: 0.22, 0.34 µg/g cr)	Adjusted	(Wallin et al. 2005)
Japan; farmers from areas with varying contamination of rice; women;	41-75 years; n=1,243	Cross-sectional; density (<80% of young adults) and biochemical markers	No effect of U-Cd (<~0.3-27 µg/g cr)	Never-smokers only	(Horiguchi et al. 2005)
South Sweden; general population; women	53-64 years; n=820	Cross-sectional; density BMDL5/BMDL10 (5%/10% additional risk) and biochemical markers	BMDL5: U-Cd 1.0 µg/g cr; BMDL10: U-Cd 1.6 µg/g cr	Stratified Association also among never-smokers	(Akesson et al. 2006; Suwazono et al. 2010)
USA, NHANES; general population; women	≥50 years; n=3,311	Cross-sectional; osteoporosis of the hip (T-score ≥2.5)	U-Cd 0.5-1.0 µg/g cr gave a 43% increased risk	Stratified. Border-line significance among never-smokers only	(Gallagher et al. 2008)
Belgium; general population; women	mean 49 years; n=294	Cross-sectional; density and biochemical markers	Negative association between U-Cd and BMD in menopause (U-Cd ≥ ~1.3 µg/g cr)	Adjusted	(Schutte et al. 2008)

31

Country; study population; sex	Age; no. of participants	Study design; bone effect measure	Threshold of bone effect	Smoking adjustment or stratification	Source
Poland; general population in polluted areas; women and men	18-76 years; n=270	Cross-sectional; density (T-Score) and biochemical markers	No association after adjustments (geometric mean U-Cd was 1.1 µg/g cr in women and 0.9 µg/g cr in men)	Adjusted	(Trzcinka-Ochocka et al. 2009)
South Sweden; general population; women	60-70 years; n=908	Cross-sectional; density and biochemical markers	Association with B-Cd (median ~0.4 µg/L)	No association in smoking-adjusted model	(Rignell-Hydbom et al. 2009)
USA, NHANES; general population; women and men	30-90 years; n=10,978	Cross-sectional; osteoporosis of the hip (T-score ≥2.5)	U-Cd 1.0-2.0 µg/g cr gave a 78% increased risk	Adjusted	(Wu et al. 2010)
Belgium; workers; men	24-64 years; n=83	Cross-sectional; osteoporosis (T-score ≥2.5)	U-Cd >1.9 µg/g cr gave a 10-fold increased risk	Adjusted	(Nawrot et al. 2010)
Sweden; general population; women	56-69 years; n=2,688	Cross-sectional; density, total body osteoporosis hip and spine (T-score ≥2.5)	U-Cd 0.50-0.75 and >0.75 compared to U-Cd <0.5 µg/g (ref); OR=1.61 (1.20–2.16) and 1.95 (1.30–2.93), respectively. In never-smokers: OR, 1.27 (0.75-2.14) and 4.24 (1.99–9.04), respectively.	Stratified. Associations in never-smokers	(Engstrom et al. 2011)
Sweden; general population; women	56-69 years; n=2,676	Prospective; density, total body osteoporosis hip and spine (T-score ≥2.5)	OR=1.32 (95% CI: 1.02-1.71) for dietary Cd > median (13 µg/d) compared to lower. Combined high dietary and U-Cd (>0.5 µg/g cr) gave OR=2.49 (95% CI: 1.71–3.63) among all women and 2.65 (95% CI: 1.43–4.91) among never-smokers	Adjusted, associations in never-smokers	(Engstrom et al. 2012)
Studies with fractures as outcome					
Belgium; general population; women and men	mean 44 years; n=506	Prospective; any fracture	Mean U-Cd 1.0 µg/g cr; RR=1.7 (1.18-2.57) for wrist fracture at a 2-fold increase of U-Cd in women, not in men. No threshold reported	No effect of smoking	(Staessen et al. 1999)

Country; study population; sex	Age; no. of participants	Study design; bone effect measure	Threshold of bone effect	Smoking adjustment or stratification	Source
China; general population in areas with varying contamination of rice; women and men	mean 50 and 55 years; n=790	Retrospective collection of low impact fractures	Mean U-Cd 9.2-13, compared to 1.6-1.8 µg/g cr caused age-standardized relative risk 4.1 (95% CI: 1.55-6.61) in men and 2.5 (95% CI: 1.42-3.54) in women	No	(Wang et al. 2003)
South Sweden; general population and workers; women and men	16-81 years; n=1,021	Retrospective; forearm fractures	HR=3.5 (CI 1.1-11) at U-Cd 2-4 compared to <0.5 µg/g cr	Adjusted	(Alfven et al. 2004)
Sweden; general population; women	56-69 years; n=2,688	Both prospective and retrospective components; any first fracture, first osteoporotic, first distal forearm	OR=2.0-2.2 comparing U-Cd >0.50 µg/g cr with lower concentrations in never-smokers. Corresponding OR for all women 1.15-1.29 (non-significant)	Stratified Associations were only statistically significant in never-smokers	(Engstrom et al. 2011)
Sweden; general population; women	56-69 years; n=2,676	Prospective for dietary Cd and combined prospective and retrospective for U-Cd; any first fracture	OR 1.31 (95% CI: 1.02-1.69) for dietary Cd > median (13 µg/d) compared to lower. Corresponding OR in never-smokers 1.54 (95% CI: 1.06-2.24). Combined high dietary and U-Cd (>0.5 µg/g cr) OR=1.46 (CI: 1.00–2.15) among all women, and 3.05 (CI: 1.66–5.59) among never-smokers	Stratified, slightly higher OR in never-smokers	(Engstrom et al. 2012)
Sweden; general population; men	45-79 years; n=22,173	Prospective; any first incident fracture, hip fractures	HR=1.2 comparing highest with lowest Cd intake tertiles	Stratified. Association for hip fracture also among never-smokers only.	(Thomas et al. 2011)

Abbreviations: bone mineral density (=density), U-Cd=urinary cadmium, cr=creatinine, RR=relative risk, OR=odds ratio, HR=hazard ratio, BMDL=benchmark dose lower confidence bound, ND=not done, CI=confidence interval. Standardized scores represent the number of standard deviations of density below the average in a population of young adults (T-score) or a population of similar age (Z-score).